

AMENDMENTS TO THE SPECIFICATION

PLEASE AMEND THE PARAGRAPH STARTING ON PAGE 8, LINE 16, AS FOLLOWS:

In an embodiment of this invention, the compounds of general formula I according to claims aspects 8 to 11 are used as preferred compounds. In this case, these are known compounds that are described in WO 97/267017. Their production can also be found in this WO publication. Surprisingly enough, it has been shown that these compounds are also very well suited as MRI-contrast media for visualization of thrombi. As quite especially preferred compounds, metal complexes MK 2, 3 and 4, as well as MK 8, 9, 10 and 11 (cf. also Table 1) are used.

Aspect is 8 is the use according to the invention, wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula I are used



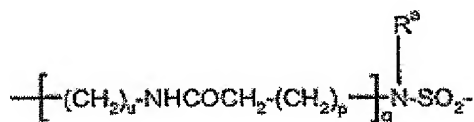
in which

R^F is a perfluorinated, straight-chain or branched carbon chain with formula -C_nF_{2n}E,

in which

E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom
and n stands for numbers 4-30,

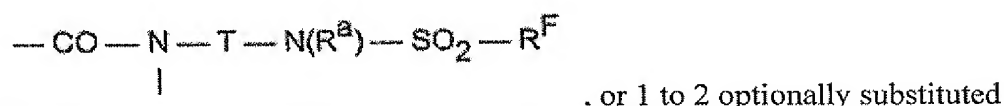
L means a direct bond, a methylene group, an -NHCO group, a group



whereby p means the numbers 0 to 10, and q and u, independently of one

another, mean numbers 0 or 1, and

R^a is a hydrogen atom, a methyl group, a benzyl group, a phenyl group, a -CH₂-OH group, a CH₂OCH₃ group, a -CH₂-CO₂H group or a C₂-C₁₅ chain, which optionally is interrupted by 1 to 3 oxygen atoms, 1 to 2 >CO groups or an optionally substituted aryl group and/or is substituted with 1 to 4 hydroxyl groups, 1 to 2 C₁-C₄ alkoxy groups, 1 to 2 carboxy groups, or a group -SO₃H-, or is a straight-chain, branched, saturated or unsaturated C₂-C₃₀ carbon chain, which optionally contains 1 to 10 oxygen atoms, 1 to 3 -NR^a groups, 1 to 2 sulfur atoms, a piperazine, a -CONR^a group, one to six -NR^aCO groups, an -SO₂ group, an -NR^a-CO₂ group, 1 to 2 CO groups, a group



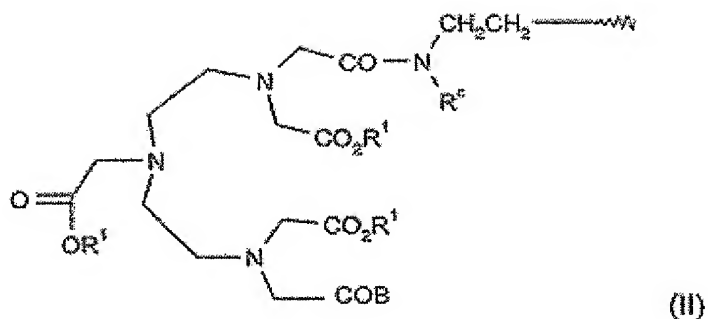
aryls and/or is interrupted by these groups and/or is optionally substituted with 1 to 3 -OR^a groups, 1 to 2 oxo groups, 1 to 2 -NH-COR^a groups, 1 to 2 -CONHR^a groups, 1 to 2 -(CH₂)_p-CO₂H groups, 1 to 2 groups -(CH₂)_p-(O)_q-CH₂CH₂-R^F,

whereby

R^a, R^F and p and q have the above-indicated meanings, and

T means a C₂-C₁₀ chain, which optionally is interrupted by 1 to 2 oxygen atoms or 1 to 2 -NHCO groups,

K stands for a complexing agent or metal complex or their salts of organic and/or inorganic bases or amino acids or amino acid amides, specifically for a complexing agent or complex of general formula II



in which R^c , R^1 and B are independent of one another, and

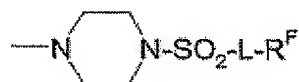
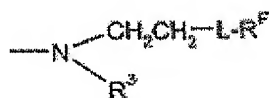
R^c has the meaning of R^a or means $-(CH_2)_m-L-R^F$, whereby m is 0, 1 or 2,

and L and R^F have the above-mentioned meaning,

R^1 , independently of one another, mean a hydrogen atom or a metal ion

equivalent of atomic numbers 22-29, 42-46 or 58-70,

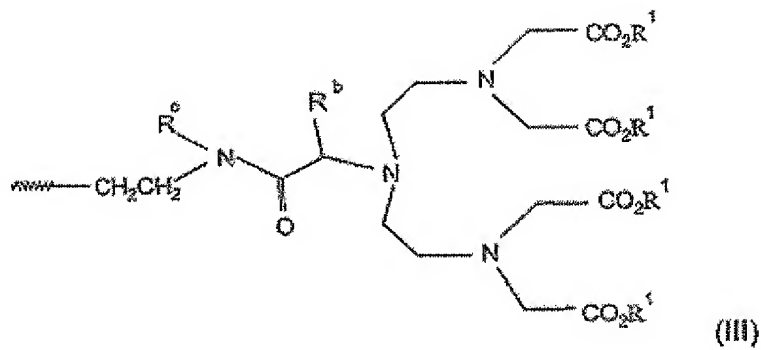
B means $-OR^1$ or



or

whereby R^1 , L, R^F and R^c have the above-mentioned meanings, or

K stands for a complexing agent or complex of general formula III

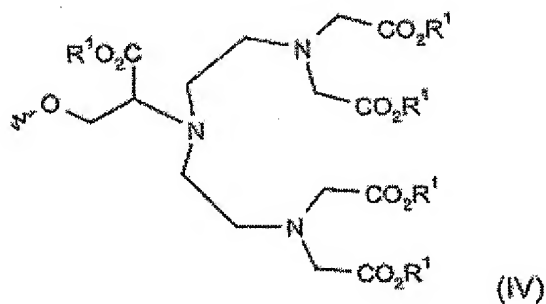


in which R^c and R^1 have the above-mentioned meanings,

R^b has the meaning of R^a ,

or

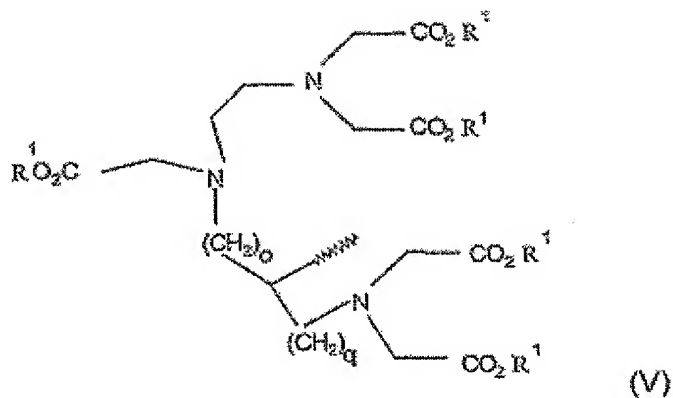
K stands for a complexing agent or complex of general formula IV



in which R^1 has the above-mentioned meaning

or

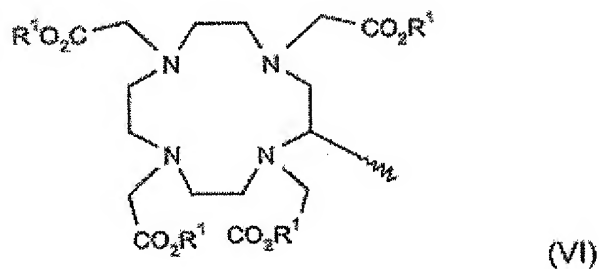
K stands for a complexing agent or complex of general formula V



in which R^1 has the above-mentioned meaning, and o and q stand for number 0 or 1, and yields the sum $o + q = 1$,

or

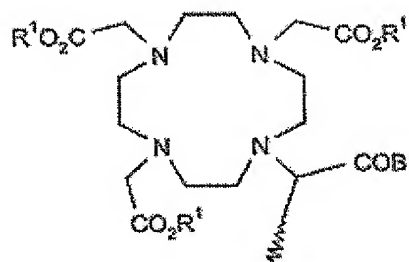
K stands for a complexing agent or complex of general formula VI



in which R^1 has the above-mentioned meaning

or

K stands for a complexing agent or complex of general formula VII

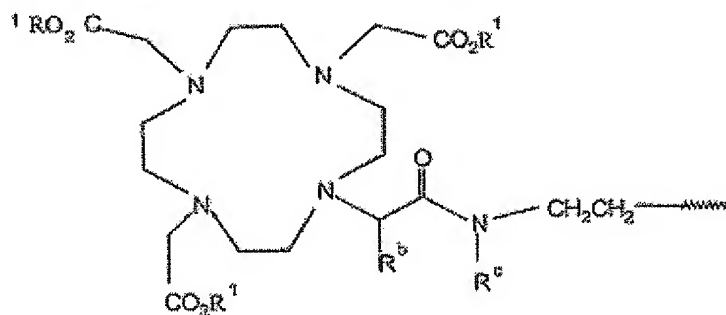


(VII)

in which R^1 and B have the above-mentioned meanings

or

K stands for a complexing agent or complex of general formula VIII

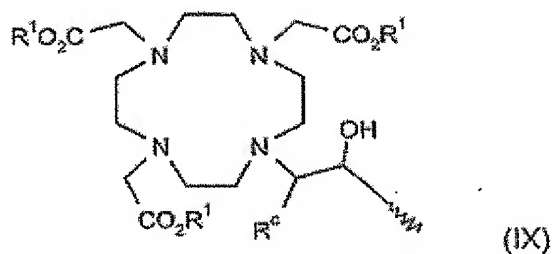


(VIII)

in which R^c and R^1 have the above-mentioned meanings, and R^b has the
above-mentioned meaning of R^a

or

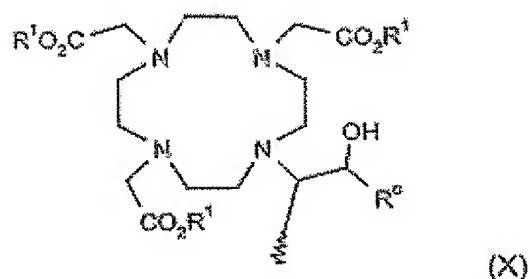
K stands for a complexing agent or complex of general formula IX



in which R^c and R^1 have the above-mentioned meanings,

or

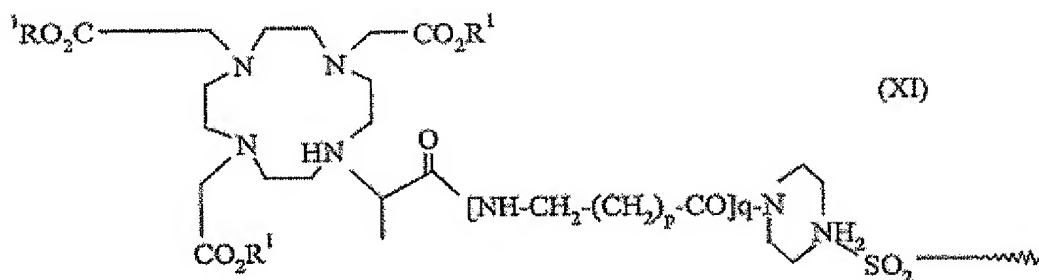
K stands for a complexing agent or complex of general formula X



in which R^c and R^1 have the above-mentioned meanings,

or

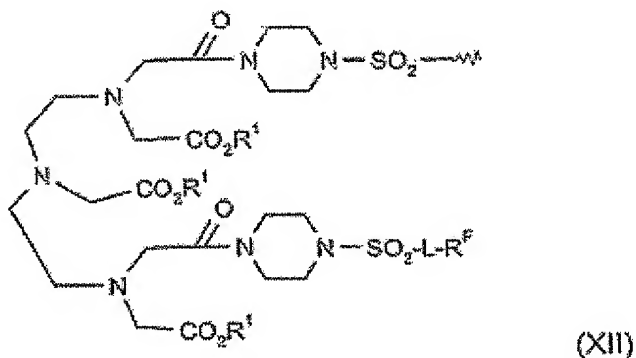
K stands for a complexing agent or complex of general formula XI



in which R^1 , p and q have the above-mentioned meaning, and R^b has the meaning of R^a .

_____ or

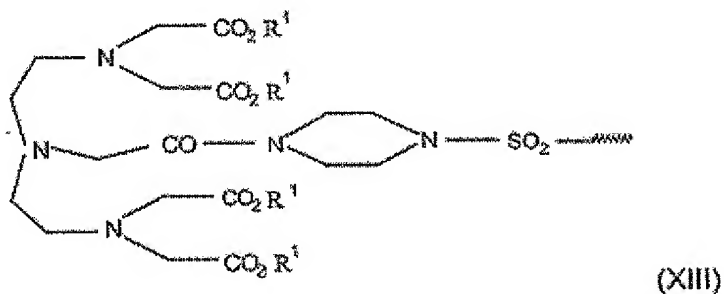
_____ K _____ stands for a complexing agent or complex of general formula XII



_____ in which L, R^F and Z^I have the above-mentioned meanings,

_____ or

_____ K _____ stands for a complexing agent or complex of general formula XIII



_____ in which R^I has the above-mentioned meaning,

are used.

_____ Aspect 9 is the use according to aspect 8, wherein the compounds of general formula I, in which L stands for

α -CH₂- β

α -CH₂CH₂- β

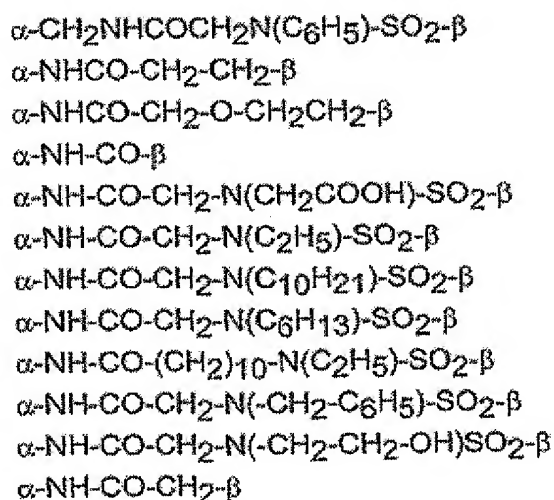
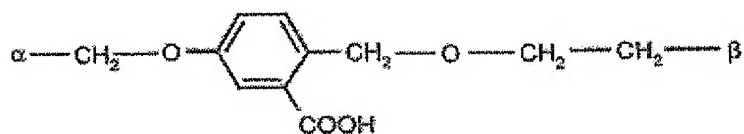
α -(CH₂)_s- β s = 3 - 15

α -CH₂-O-CH₂CH₂- β

α -CH₂-(O-CH₂-CH₂)_t- β t = 2 - 6

α -CH₂-NH-CO- β

α -CH₂-NH-CO-CH₂-N(CH₂COOH)-SO₂- β



α -CH₂-O-C₆H₄-O-CH₂-CH₂- β
 α -CH₂-C₆H₄-O-CH₂-CH₂- β
 α -N(C₂H₅)-SO₂- β
 α -N(C₆H₅)-SO₂- β
 α -N(C₁₀H₂₁)-SO₂- β
 α -N(C₆H₁₃)-SO₂- β
 α -N(C₂H₄OH)-SO₂- β
 α -N(CH₂COOH)-SO₂- β
 α -N(CH₂C₆H₅)-SO₂- β
 α -N-[CH(CH₂OH)₂]-SO₂- β
 α -N-[CH(CH₂OH)CH(CH₂OH)]-SO₂- β

and in which α represents the binding site to the complexing agent or metal complex K, and β represents the binding site to the fluorine radical,
are used.

Aspect 10 is the use according to aspects 8 and/or 9, wherein the compounds of formula I in which n in formula -C_nF_{2n}E stands for numbers 4-15 and/or E in this formula means a fluorine atom are used.

Aspect 11 is the use according to one of aspects 8 to 10, wherein the following compounds are used:

- Gadolinium complex of 10-[1-methyl-2-oxo-3-aza-5-oxo-{4-perfluorooctylsulfonyl-piperazin-1-yl}-pentyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17-heptafluoroheptadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5,9-dioxo-9-{4-perfluorooctyl}-piperazin-1-yl}-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluorooctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,

- Gadolinium complex of 10-[2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluorotetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-henicosafuoro-nonadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-11-aza-11-(perfluorooctylsulfonyl)-tridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluorooctylsulfonyl)-8-phenyl-octyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraaza-cyclododecane.

PLEASE AMEND THE PARAGRAPH STARTING ON PAGE 8, LINE 22, AS FOLLOWS:

In another embodiment of this invention, those compounds of general formula Ia according to ~~claims~~ aspects 12 to 21 are used as preferred compounds. These compounds are known and are described in WO 99/01161. Their use as MRI contrast media for visualization of thrombi still had not been described to date. Of these compounds, quite especially preferably metal complex MK 12 (cf. Table 1) is used.

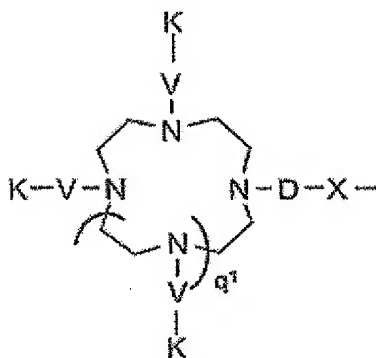
Aspect 12 is the use according to the invention, wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula Ia are used



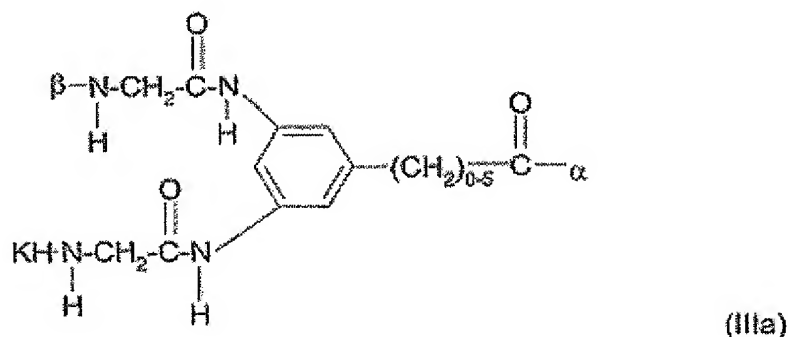
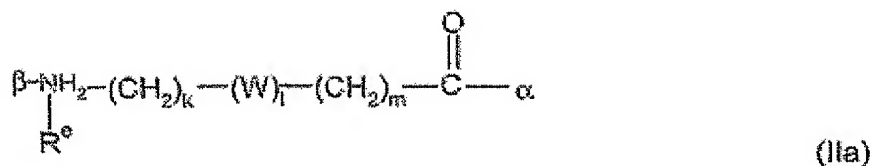
in which

- A is a molecule part that contains 2 to 6 metal complexes, which are bonded directly or via a linker to a nitrogen atom of an annular skeleton chain,
- and

- R^F is a perfluorinated, straight-chain or branched carbon chain with formula $-C_nF_{2n}E$, in which E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom, and n stands for numbers 4-30, whereby molecule part A has the following structure:



- whereby
- q^1 is a number 0, 1, 2 or 3,
 - K stands for a complexing agent or metal complex or their salts of organic and/or inorganic bases or amino acids or amino acid amides,
 - X is a direct bond to the perfluoroalkyl group, a phenylene group or a C_1 - C_{10} -alkylene chain, which optionally contains 1-15 oxygen atoms, 1-5 sulfur atoms, 1-10 carbonyl groups, 1-10 (NR^d) groups, 1-2 NR^dSO_2 groups, 1-10 $CONR^d$ groups, 1 piperidine group, 1-3 SO_2 groups and 1-2 phenylene groups or optionally is substituted by 1-3 radicals R^F , in which R^d stands for a hydrogen atom, a phenyl group, benzyl group or a C_1 - C_{15} alkyl group, which optionally contains 1-2 $NHCO$ groups, 1-2 CO groups, or 1-5 oxygen atoms and optionally is substituted by 1-5 hydroxy, 1-5 methoxy, 1-3 carboxy, or 1-3 R^F radicals,
 - V is a direct bond or a chain of general formula IIa or IIIa:



in which

■ R^e is a hydrogen atom, a phenyl group, a benzyl group or a C_1 - C_7 -alkyl group, which optionally is substituted with a carboxy group, a methoxy group or a hydroxy group,

■ W is a direct bond, a polyglycol ether group with up to 5 glycol units, or a molecule part of general formula IVa



in which R^h is a C_1 - C_7 carboxylic acid, a phenyl group, a benzyl group or a $\text{-(CH}_2\text{)}_{1-5}\text{-NH-K}$ group,

■ α represents the binding to the nitrogen atom of the skeleton chain, β represents the binding to complexing agents or metal complex K,

■ and in which variables k and m stand for natural numbers between 0 and 10, and l stands for 0 or 1

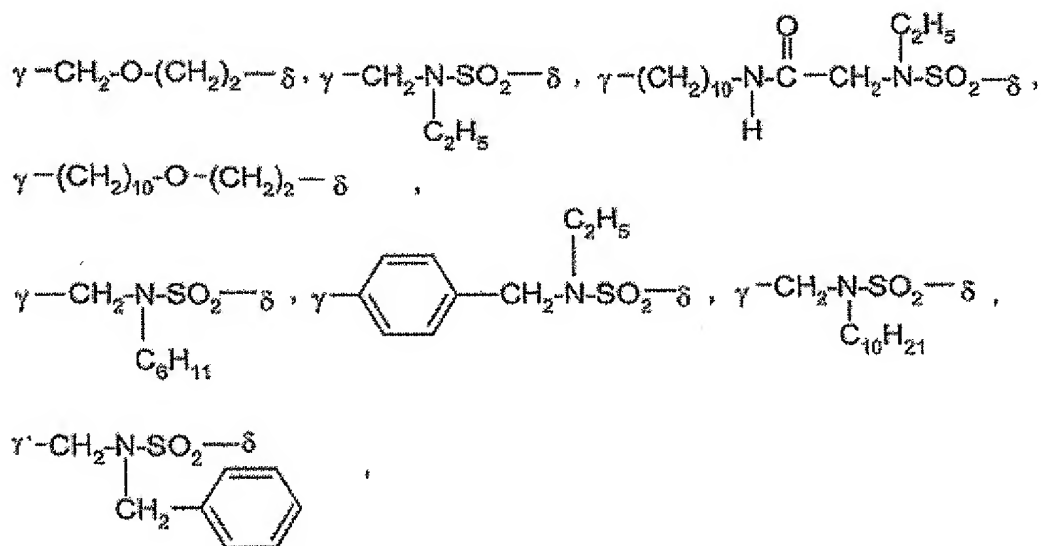
and whereby

o D is a CO or SO₂ group,

are used.

Aspect 13 is the use according to aspect 12, wherein the compounds of general formula Ia in which q is the number 1 are used.

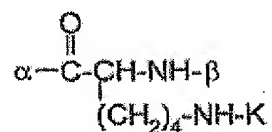
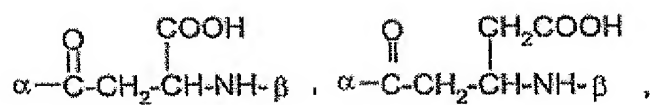
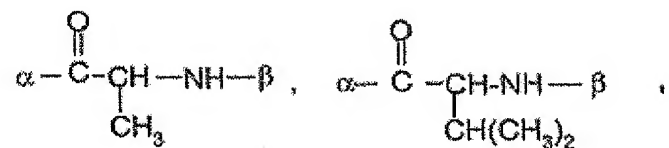
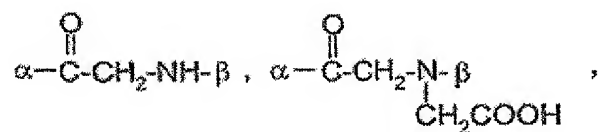
Aspect 14 is the use according to aspect 12, wherein the compounds of general formula Ia are used, in which molecule part X is an alkylene chain, which contains 1-10 CH₂CH₂O groups or 1-5 COCH₂NH groups, a direct bond or one of the following structures



whereby

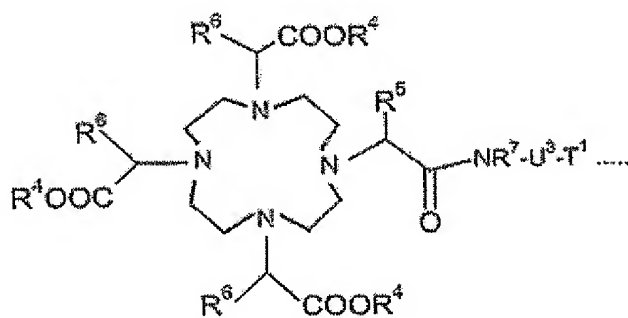
γ binds to D , and δ binds to R^F .

Aspect 15 is the use according to aspect 12, wherein the compounds of general formula Ia, in which V is a molecule part with one of the following structures

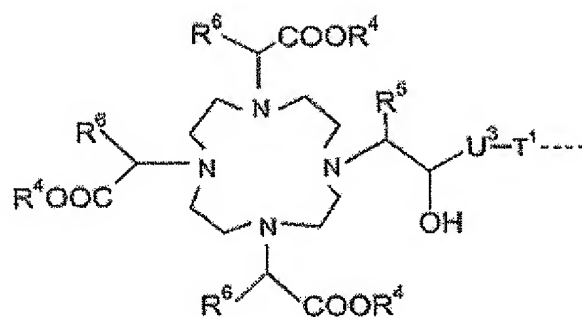


are used.

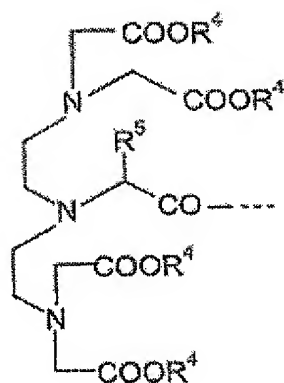
Aspect 16 is the use according to aspect 12, wherein the compounds of general formula Ia, in which K represents a complex of general formula Va, VIa, VIIa or VIIIa,



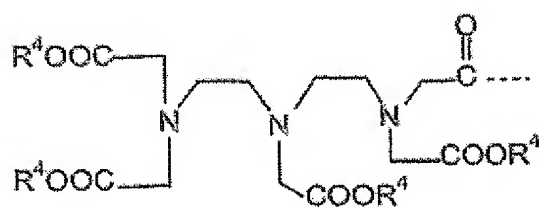
(Va)



(VIa)



(VIIa)



(VIIIa)

are used,

whereby

- R^4 , independently of one another, are a hydrogen atom or a metal ion equivalent

of the elements of atomic numbers 23-29, 42-46 or 58-70,

- R⁵ is a hydrogen atom or a straight-chain, branched, saturated or unsaturated C₁-C₃₀ alkyl chain, which optionally is substituted by 1-5 hydroxy, 1-3 carboxy or 1 phenyl group(s) and/or optionally is interrupted by 1-10 oxygen atoms, 1 phenylene group or 1 phenylenoxy group,
- R⁶ is a hydrogen atom, a straight-chain or branched C₁-C₇ alkyl radical, a phenyl radical or a benzyl radical,
- R⁷ is a hydrogen atom, a methyl group or ethyl group, which optionally is substituted by a hydroxy group or carboxy group,
- U³ is a straight-chain, branched, saturated or unsaturated C₁-C₂₀ alkylene group optionally containing 1-5 imino groups, 1-3 phenylene groups, 1-3 phenylenoxy groups, 1-3 phenylenimino groups, 1-5 amide groups, 1-2 hydrazide groups, 1-5 carbonyl groups, 1-5 ethylenoxy groups, 1 urea group, 1 thiourea group, 1-2 carboxyalkylimino groups, 1-2 ester groups, 1-1-0 oxygen atoms, 1-5 sulfur atoms and/or 1-5 nitrogen atoms, and/or optionally substituted by 1-5 hydroxy groups, 1-2 mercapto groups, 1-5 oxo groups, 1-5 thioxo groups, 1-3 carboxy groups, 1-5 carboxyalkyl groups, 1-5 ester groups and/or 1-3 amino groups, whereby the optionally contained phenylene groups can be substituted by 1-2 carboxy groups, 1-2 sulfone groups or 1-2 hydroxy groups
- T¹ stands for a -CO-β, -NHCO-β or -NHCS-β group, whereby β represents the binding site to V.

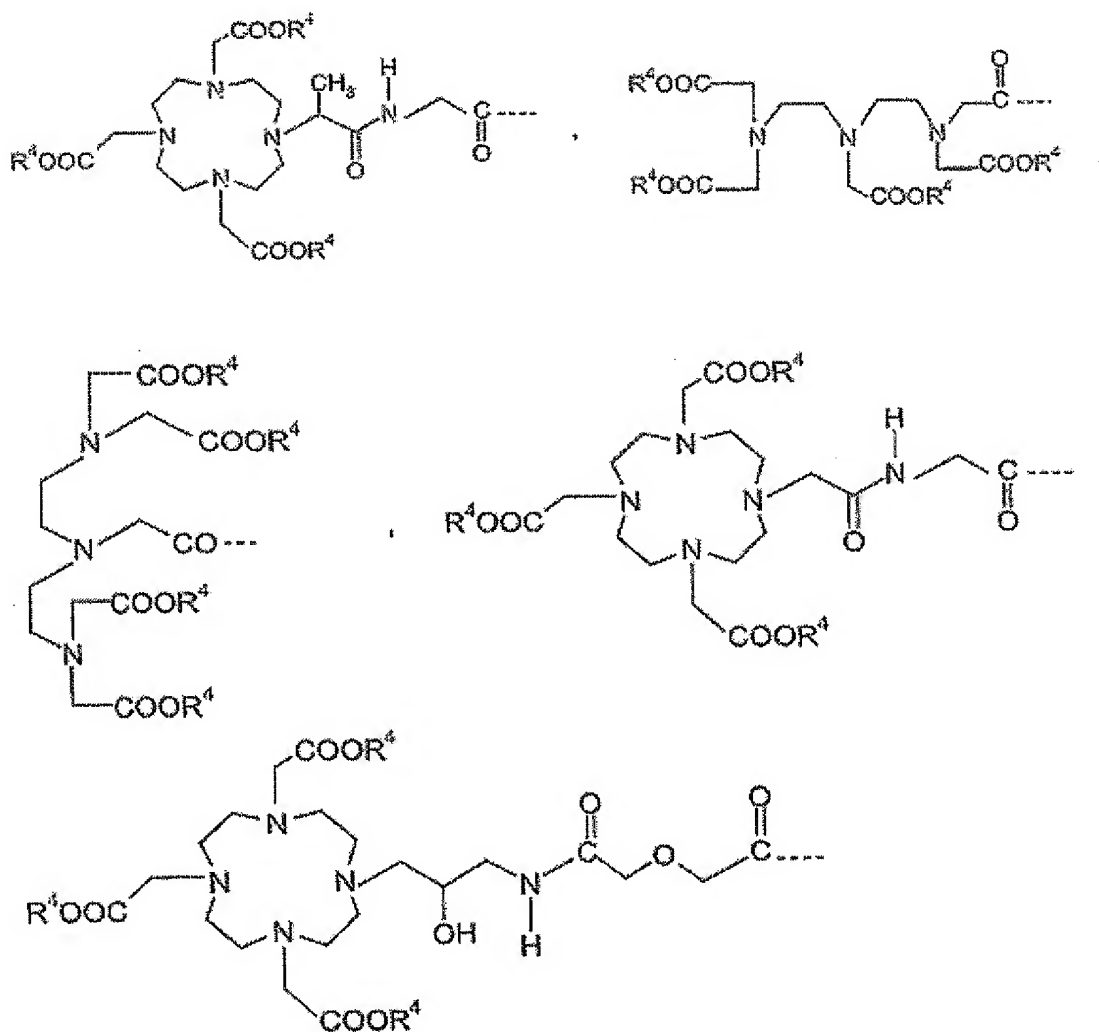
Aspect 17 is the use according to aspect 16, wherein the C₁-C₂₀-alkylene chain that stands for U³ contains the groups -CH₂NHCO-, -NHCOCH₂O-, -NHCOCH₂OC₆H₄-, -N(CH₂CO₂H)-, -CH₂OCH₂-, -NHCOCH₂C₆H₄-, -NHCSNHC₆H₄-, -CH₂OC₆H₄-, -CH₂CH₂O- and/or is substituted by the groups -COOH and -CH₂COOH.

Aspect 18 is the use according to aspect 16, wherein U³ stands for a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -C₆H₄-, -C₆H₁₀-, -CH₂C₆H₄-, -CH₂NHCOCH₂CH(CH₂CO₂H)-C₆H₄-, -

CH₂NHCOCH₂OCH₂-, or

-CH₂NHCOCH₂C₆H₄- group.

Aspect 19 is the use according to aspect 12, wherein the compounds of general formula Ia in which K has one of the following structures:



are used.

Aspect 20 is the use according to one of aspects 12 to 19, wherein the compounds of general formula Ia in which the perfluoroalkyl chain R^F is $-\text{C}_6\text{F}_{13}$, $-\text{C}_8\text{F}_{17}$, $-\text{C}_{10}\text{F}_{21}$ or $-\text{C}_{12}\text{F}_{25}$ are used.

Aspect 21 is the use according to one of aspects 12 to 20, wherein the gadolinium complex of 1,4,7-tris{1,4,7-tris(N-(carboxylatomethyl)-10-[N-1-methyl-3,6-diaza-2,5,8-trioxooctane-1,8-diyl])-1,4,7,10-tetraazacyclododecane, Gd complex}-10-[N-2H,2H,4H,4H,5H,5H-3-oxa-perfluorotridecanoyl]-1,4,7,10-tetraazacyclododecane is used.